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## Note

# Synthesis of 5-oxo-5*H*-[1]-benzopyrano-[2,3-*b*]pyridine derivatives

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Five compounds of 2,3-cylic substituted 5-oxo-5*H*-[1]-benzopyrano[2,3-*b*]pyridine derivatives **3** have been synthesized by the reaction of substituted 4-oxo-4*H*-[1]-benzopyran-3-carbonitriles with 5,5-dimethyl-1,3-cyclohexanedione or 1,3-cyclohexanedione in the presence of piperidine.

It has been reported that 5-oxo-5*H*-[1]-benzopyrano[2,3-*b*]pyridine derivatives are highly potent inhibitors of the passive cutaneous anaphylaxis[1,2]. Nohara *et al.* has reported that a massive research effort had been expanded upon the chemistry of benzopyrano[2,3-*b*]pyridine with particular emphasis on the synthesis of new compounds for pharmacological screening. Since then derivatives of benzopyrano[2,3-*b*]pyridine have been synthesized[3-5]. But there is no report on the synthesis of 2,3-cyclic substituted 5-oxo-5*H*-[1]-benzopyrano[2,3-*b*]pyridine derivatives **3**. With a view to studying structural activity relationship, we report herein the synthesis of **3**. The synthetic route is outlined in **Scheme I.**

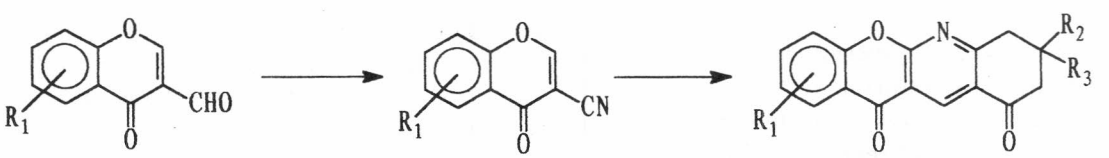
The starting materials 4-oxo-4*H*-[1]-benzopyran-3-carboxyaldehydes **1** were prepared from *o*-hydroxybenzoacetone by the method of Vilsmeier-Hacck reaction[6]. The reaction of **1b, 1c** with hydroxyamine hydrochloride in 95% ethanol in the presence of hydrochloric acid afforded in one-step the 4-oxo-4*H*-[1]-benzopyran-3-carbonitrile derivatives **2b, 2c**. In the case of **1a**, the isolated oxime was converted to the nitrile derivative **2a** by refluxing with acetic anhydride[7].

Reactions of substituted 4-oxo-4*H*-[1]-benzopyran-3-carbonitrile with some reactive methylene compounds afforded 2,3-disubstituted-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine derivatives[3-5]. The reaction of carbonitriles **2** with 5,5-dimethyl-1,3-cyclohexanedione and 1,3-cyclohexanedione in anhydrous ethanol in the presence of piperidine furnished 2,3-cyclic substituted-5-oxo-5*H*-[1]-benzopyrano[2,3-*b*]pyridine derivatives **3**.

### Experimental Section

Melting points were uncorrected. IR spectra ($\upsilon_{max}$ in $cm^{-1}$) were recorded on PE983 spectrometer by using KBr pellets; $^1H$ NMR spectra in $CDCl_3$ on Bruke-Ac-E200 spectrometer (chemical shifts in $\delta$, ppm) and mass spectra on HP5988A spectrometer. Elementary analysis were conducted on Caro Erba 1106 instrument.

**6-Methoxycarbonyl-4-oxo-4*H*-[1]-benzopyran-3-carbonitrile 2a.** A mixture of **1a** (3 g, 13 mmoles),




1a. $R_1$=6-COOMe
1b. $R_1$=5-OMe
1c. $R_1$=5-OH

3a. $R_1$=8-COOMe,$R_2$=$R_3$=Me
3b. $R_1$=8-COOMe,$R_2$=$R_3$=H
3c. $R_1$=7-OMe,$R_2$=$R_3$=Me
3d. $R_1$=7-OH,$R_2$=$R_3$=Me
3e. $R_1$=7-OH,$R_2$=$R_3$=H

**Scheme I**

95% EtOH (50 mL), and hydroxylamine hydrochloride (0.9 g, 13 mmoles) was heated at 80°C for 4 hr. The resulting solution was concentrated and the residue dissolved in $Ac_2O$ (30 mL). The solution was heated at 130°C for 3 hr. After evaporation of $Ac_2O$, the residue was recrystallized from benzene to afford **2a** as white needles (1.2 g, 40%), m.p. 173-75°; IR: 2244, 1734, 1668 $cm^{-1}$; $^1H$ NMR($CDCl_3$): 8.91 (d, 1H, *J*=2.16 Hz, 5-H), 8.41 (dd, 1H, *J*=8.66, 2.1 Hz, 7-H), 8.43 (s, 1H, 2-H), 7.60 (d, 1H, *J*=8.70 Hz, 8-H), 3.97 (s, 3H, $-COOCH_3$); MS (EI, m/z): 229 ($M^+$), 198, 170.

**6-Methoxy-4-oxo-4*H*-[1]-benzopyran-3-carbonitrile 2b.** A mixture of 5-methoxyl-4-oxo-[1]-benzopyran-3-carboxaldehyde (2 g, 9.8 mmoles), hydroxyamine hydrochloride (0.68 g, 9.8 mmoles), 95% EtOH (10 mL), and concentrated HCl (1 mL) was refluxed for 12 hr with stirring. After cooling, the precipitates were collected by filtration and recrystallized from EtOH to afford **2b** as pale yellow crystals (1.1 g, 55.8%), m.p. 156-58°; IR: 2233, 1669 $cm^{-1}$; $^1H$ NMR($CDCl_3$): 8.25 (s, 1H, 2-H), 7.65 (t, 1H, *J*=8.4 Hz, 7-H), 7.05 (d, 1H, *J*=8.4 Hz, 6-H), 6.90 (d, 1H, *J*=8.4 Hz, 8-H), 3.97 (s, 3H, $OCH_3$); MS (EI, m/z): 201, 173.

**6-Hydroxyl-4-oxo-4*H*- [1]-benzopyran-3-carbonitrile 2c.** It was prepared as **2b** above, m.p.: 148-50°; IR: 3243, 2240 (CN), 1644, 1612, 1461 $cm^{-1}$; $^1H$ NMR($CDCl_3$): 11.62 (s, 1H, 5-OH), 8.37 (s, 1H, 2-H), 7.64 (t, 1H, *J*=8.2 Hz, 7-H), 7.01 (d, 1H, 8.2 Hz, 6-H), 6.95 (d, 2H, *J*=8.2 Hz, 8-H); MS (EI, m/z): 187, 159.

**1,2,3,4-Tetrahydro-8-methoxycarbonyl-2,2-dimethyl-6*H*-[1]-benzopyrano[2,3-*b*]quinoline-4,6-dione 3a.** A mixture of **2a** (100 mg, 0.439 mmoles), 5,5-dimethyl-1,3-cyclohexanedione (61 mg, 0.439 mmoles), piperidine (3 drops), and EtOH (1.5 mL) was refluxed for 7 hr and cooled. The separated solid was collected by filtration, washed with EtOH, and recrystallized from DMF-EtOH to afford **3a** as white needles (120 mg, 78.3%), m.p.: 196-98°; IR: 1721, 1672, 1600, 1549 $cm^{-1}$; $^1H$ NMR($CDCl_3$): 9.25 (s, 1H, 5-H), 8.98 (d, 1H, *J*=2.17 Hz, 7-H), 8.44 (dd, 1H, *J*=8.8, 2.17 Hz, 9-H), 7.67 (d, 1H, *J*=8.8 Hz, 10-H), 3.97 (s, 3H, $-COOCH_3$), 3.14 (s, 2H, 1-H), 2.64 (s, 2H, 3-H), 1.15 (s, 6H, 2-$CH_3$×2); MS (EI, m/z): 351, 336, 323. Anal. Calcd. for $C_{20}H_{17}NO_5$: C, 68.38; H, 4.84; N, 3.99. Found: C, 68.23; H, 4.86; N, 3.92%.

**1,2,3,4-Tetrahydro-8-methoxycarbonyl-6*H*-[1]-benzopyrano[2,3-*b*]quinoline-4,6-dione 3b.** A mixture of **2a** (100 mg, 0.439 mmoles), 1,3-cyclohexanedione (50 mg, 0.439 mmoles), piperidine (3 drops), and EtOH (1.5 mL) was refluxed for 7 hr and cooled. The solid was removed by filtration, filtrate was concentrated *in vacuo*, and the residue was chromatographed on silica gel using acetone-petroleum as eluent. **3b** was obtained as white crystals (100 mg, 72%), m.p. 302-4°; IR: 1724, 1672, 1604 $cm^{-1}$; $^1H$ NMR($CDCl_3$): 9.29 (s, 1H, 5-H), 8.98 (d, 1H, *J*=2 Hz, 7-H), 8.43 (dd, 1H, *J*=8.7 Hz, 2 Hz, 9-H), 7.64 (d, 2H, *J*=8.7 Hz, 10-H), 3.98 (s, 3H, $-COOCH_3$), 3.27 (t, 2H, *J*=6.2 Hz, 1-H), 2.79 (t, 2H, *J*=6.2 Hz, 3-H), 2.28 (pent, 2H, *J*=6.2 Hz, 2-H); MS (EI, m/z): 323 ($M^+$), 295, 292, 264.

**1,2,3,4-Tetrahydro-7-methoxy-2,2-dimethyl-6*H*-[1]-benzopyrano[2,3-*b*]quinoline-4,6-dione 3c.** A mixture of **2b** (200 mg, 1 mmoles), 5,5-dimethyl-1,3-cyclohexanedione (140 mg, 1 mmoles), piperidine (0.2 mL), and EtOH (2 mL) was refluxed for 7 hr and cooled. The solution was concentrated *in vacuo*, and the residue was chromatographed on silica gel using acetone-petroleum as eluent. **3c** was obtained as yellow crystals (200 mg, 62%), m.p.: 208-10°; IR: 1684, 1656, 1591 $cm^{-1}$; $^1H$ NMR($CDCl_3$): 9.20 (s, 1H, 5-H), 7.66 (t, 1H, *J*=8.4 Hz, 9-H), 7.15 (d, 1H, *J*=8.4 Hz, 8-H), 6.87 (d, 1H, *J*=8.4 Hz, 10-H), 4.03 (s, 3H, $OCH_3$), 3.1 (s, 2H, 1-H), 2.6 (s, 2H, 3-H), 1.14 (s, 6H, 2-$CH_3$×2); MS (EI, m/z): 323 ($M^+$), 308, 294, 277.

**1,2,3,4-Tetrahydro-7-hydroxy-2,2-dimethyl-6*H*-[1]-benzopyrano[2,3-*b*]quinoline-4,6-dione 3d.** A mixture of **2c** (100 mg, 0.53 mmoles), 5,5-dimethyl-1,3-cyclohexanedione (75 mg, 0.53 mmoles), piperidine (3 drops), and EtOH (2 mL) was refluxed for 7 hr and cooled. The solution was concentrated *in vacuo*, and the residue was chromatographed on silica gel using acetone-petroleum as eluent. **3d** was obtained as pale yellow needles (70 mg, 43%), m.p. 232-34°; IR: 1685, 1641, 1616 $cm^{-1}$; $^1H$ NMR($CDCl_3$): 12.19 (s, 1H, 7-OH), 9.21 (s, 1H, 5-H), 7.85 (t, 1H, *J*=6.3 Hz, 9-H), 7.0 (d, 1H, *J*=8.2 Hz, 8-H), 6.9 (d, 1H, *J*=8.2 Hz, 10-H), 3.13 (s, 2H, 1-H), 2.83 (s, 2H, 3-H), 1.15 (s, 6H, 2-$CH_3$×2); MS (EI, m/z): 309 ($M^+$), 253, 223. Anal. Calcd. for $C_{18}H_{15}NO_4$: C, 69.90; H, 4.84; N, 4.53. Found: C, 69.89; H, 4.69; N, 4.59%.

**1,2,3,4-Tetrahydro-7-hydroxy-6*H*-[1]-benzopyrano[2,3-*b*]quinoline-4,6-dione 3e.** A mixture of **2b** (100 mg, 0.53 mmoles), 1,3-cyclohexanedione (60

mg, 0.53 mmoles), piperidine (0.2 mL), and EtOH (2 mL) was refluxed for 7 hr and cooled. The solution was concentrated *in vacuo* and the residue was chromatographed on silica gel using acetone-petroleum as eluent **3e** was obtained as pale yellow needles (61 mg, 41%), m.p.: 218-20°; IR: 1689, 1642, 1589 $cm^{-1}$; $^1H$ NMR($CDCl_3$): 12.17 (s, 1H, 7-OH), 9.22 (s, 1H, 5-H), 7.65 (t, 1H, *J*=8.3 Hz, 9-H), 7.03 (d, 1H, *J*=8.2 Hz, 8-H), 6.87 (d, 1H, *J*=8.3 Hz, 10-H), 3.25 (t, 2H, *J*=6.2 Hz, 2-H), 2.78 (t, 1H, *J*=6.2 Hz, 4-H), 2.28 (m, 2H, 3-H): MS (EI, m/z): 281 ($M^+$) 253, 225, 196.

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